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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,462	05/05/2006	Makrina Savvidou	HO-P03236US0	8934

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,462	SAVVIDOU ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims filed November 21, 2008 have been received and entered. Claims 1, 6-8 have been amended, while claims 2-3, 12-28 have been canceled. Claims 1, 4- 11 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/21/2008 has been entered.

Election/Restrictions

Applicant's election without traverse of claims 1-2 and 4-11 in the reply filed on August 31, 2007 was acknowledged.

Claims 1-2, 4-10 and 11 are under consideration.

Declaration

The Rose declaration filed on November 21, 2008 under 37 CFR 1.132 is sufficient in part to overcome the rejection of claims 1, 4-11, applied under 35 U.S.C. 112 First paragraph. The declaration will be discussed in detail below as it applies to the rejection.

Maintained in modified form-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining that a pregnant woman is at risk of developing pre-eclampsia or whether that her fetus is at risk of developing intrauterine growth restriction (IUGR), which method comprises: (a) measuring plasma concentration of asymmetric dimethylarginine (ADMA) in a pregnant woman at risk of developing pre-eclampsia or her fetus being at risk of developing IUGR at a stage of pregnancy from 23 to 25 weeks gestation; and (b) plasma ADMA level in said women greater than 1.5 microM/L indicates that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR, does not reasonably provide enablement for determining that a pregnant woman is at risk of developing pre-eclampsia by measuring ADMA at any other stage of pregnancy or measuring ADMA levels in the any tissue or body fluid of a pregnant woman. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance

provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

As an initial matter, it is noted that rejections to the claims have been modified in view of applicants' amendments and declaration by Dr. Rose to indicate the enabling embodiment. Applicants argue, and cite the declaration filed by Dr. Rose, to assert that an elevated ADMA level can be used to identify pregnant woman as being at risk of developing pre-eclampsia or their fetuses as being at risk of developing IUGR. Applicants assert that prior art cited before the filing of instant application fails to provide evidence for the lack of evidence for the lack of predictability. Applicants assert that Cook reference teaches ADMA level posses the degree of predictability for using ADMA as marker. The Rose declaration states "... the invention is a "risk test". Women who display an ADMA level greater than 1.5 micro mol/L at 4 to 25 weeks gestation will be placed in a high risk bracket and monitored further for any signs of pre-eclampsia or IUGR" (see declaration section 2). It is further suggested that the claimed methods are drawn to a predicting risk and not to diagnose pre-eclampsia. The declaration further discusses that ADMA level of greater then 1.5 micro mol/L is indicative of the women being at risk of developing pre-eclampsia (see declaration section 3-4 and 7).

Applicants' arguments filed on November 21, 2008 have been fully considered but they are not fully persuasive. In response, Examiner would generally agree with the applicants' assertion that the claimed method is directed to determining

whether a pregnant woman is at risk of developing pre-eclampsia (PE) or IUGR, which is different from diagnosing PE or IUGR. However, in the instant case the analysis is based on the predictability of the risk of developing PE or IUGR is based on the presence of ADMA level greater then 1.5 μmol/L at any stage of pregnancy in any tissue/fluid. It is noted that applicants agree that pre-eclampsia is a multi factorial disease, which involves changes in, amongst others, a cardiovascular function, metabolic function and renal function (see Cooke et al Circulation. 2004 Apr 20;109(15):1813-8, Fard et al, Arterioscler Thromb Vasc Biol 2000; 20: 2039-2044 and Kielstein et al Am J Kidney Dis. 2005; 46: 186–202, Fang et al Hypertension 2006; 48: 724-729, all of the record). Thus, the state of art teaches level of ADMA may be influenced under different condition and disorders and may not be specific risk marker for PE or IUGR. The guidance provided in the specification shows ADMA level greater than 1.5 microM/L at 23 to 25 weeks of gestation indicates risk of developing pre-eclampsia or risk of developing IUGR in pregnant women.

The claims embrace a method of determining that a pregnant woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing IUGR by measuring asymmetric dimethylarginine (ADMA) levels in the any tissue or body fluid of a pregnant woman of varying gestational age (4-25 week of gestation). Subsequent claims limit the gestational age to include 10 to 25 or 15 -25 weeks of gestation. The specification teaches women with bilateral notches had significantly higher levels of ADMA compared to the women with normal uterine artery Doppler waveforms (2.4 μmol/L vs. 0.81 μmol/L respectively, Figure 2, page 21) which is at least three time of normal pregnancy level. With respect to applicants' argument that the data demonstrates that a plasma ADMA level measurement of greater than 1.5 micro mol/L can be used determine that a woman is at risk of developing IUGR or pre-eclampsia (see page 6 of the argument), it is noted that the specification discloses that women who subsequently developed pre-eclampsia had

significantly higher levels of ADMA compared to the women who had normal pregnancies (Table 3). In fact, Savvidou et al (Lancet, 2003 May 3:361(9368):1511-7, IDS) in a post filing art states" [d]uring a healthy pregnancy, maternal ADMA concentration falls until up to 24 weeks' gestation before rising to pre pregnancy concentrations towards term. This change mirrors the initial fall and subsequent rise in maternal vascular tone and blood pressure during normal gestation". It is noted that although ADMA concentrations have previously been shown to be raised in established pre-eclampsia (see Holden et al *Am J Obstet Gynecol* 178 (1998), pp. 551–556, art of record), instant application differs by showing existence of high ADMA concentrations in women at 23-25 weeks gestation with abnormal uterine artery doppler waveforms. Additionally, specification teaches that not all women with raised concentrations of ADMA developed pre-eclampsia (see table 3), rather women with notches and a high ADMA developed pre-eclampsia. In the instant case, there is no evidence on record that establishes nexus between higher ADMA level in any tissue or fluid of a pregnant woman at a first trimester stage of pregnancy from 4 to 15 weeks gestation. In fact, Ellis et al (Acta Obstet Gynecol Scand. 2001 Jul;80(7):602-8, IDS) report no convincing correlations between ADMA and clinical parameters (see page 606, col. 1, para. 1). Furthermore, Contrary to the limitation of claim 7, Ellis et al teach that the ADMA/SDMA quotient is significantly lower in subjects with severe preeclampsia than in controls, reflecting a marked elevation of SDMA. These results are also contrary to the teaching of Pettersson et al (Acta Obstet Gynecol Scand 1998; 77: 808–813). In view of foregoing it is apparent that prior art generally reported variable range of ADMA level at same gestational age and also reported contradictory effect of ADMA or ADMA/SDMA ratio in predicting any clinical outcome. The unpredictability of establishing nexus between first trimester uterine artery resistance and maternal serum concentration of ADMA is further evidenced by a recent report that states "[n]o significant difference was found in maternal serum ADMA between

pregnancies with first trimester high resistance uterine artery blood flow and control" (abstract) (Prefumo et al Ultrasound Obstet Gynecol, 2008, 31, 153-157). It is emphasized that several years after filing of this report Prefumo concludes that a long longitudinal study would be required to examine whether concentration of maternal ADMA in the first trimester co relates with the onset of the pre-eclampsia (se page 156, col. 1, last para.)

MPEP 2164.05(a) also states "If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993)* an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animals were held nonenabled.

Therefore, it is evident from the teaching of the cited references filed before, and after filing of this application show measuring ADMA level at different stage of pregnancy would not shows the ADMA level greater than 1.5 micro mol/L as argued by the applicants (see arguments page 6, last para.). Artisan could not predict, in the absence of proof to the contrary, that such a method would be efficacious in the predicting risk of developing IUGR or pre-eclampsia in any pregnant by measuring ADMA level in plasma at a stage of pregnancy from 23 -25 week gestation. An artisan would have to carry out an extensive experimentation to make and use the invention, and such experimentation would have been undue because of the art of predicting risk for developing pre eclampsia or its fetus developing IUGR by measuring the levels of ADMA, a single biomarker at any stage of pregnancy is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced commensurate with the full scope of the claims.

Applicants also argue that a working example is given in the specification describing how to practice the invention in a pregnant woman. One of ordinary skill in the art through routine optimization could easily identify which tissue or fluid

would be optimal for monitoring ADMA levels (see applicants' argument page 7, last para. and page 8, para. 1).

In response, it is emphasized that the claims are directed to measuring ADMA levels in any tissue or fluid of a pregnant women that is limited by determining that women is at risk of developing IUGR or PE if the level of ADMA is greater than 1.5 micro mol/L. Examiner had previously indicated that the state of the art generally recognized that the reference used for comparison with the test level of the AMDA level may vary, depending on aspect of the invention being practiced. These values are subjective to sample population, other variables (age, gender, hormonal status, ethnicity, disease state), assay system and are subjective to different interpretation by different artisans (see López -Jaramillo (J Hypertens. 2005; 23(6): 1121-9 and references therein, art of record). The specification contemplates that the sample typically comprises a body fluid of the woman. The sample is preferably a blood, plasma, serum or urine sample but may be amniotic fluid (see page 5, line 30-31 of the specification). It is noted that Bulau et al (American Journal of Lung Cell Mol. Physiol, 2007, 292, L18-L24) reported varying level of ADMA in different tissue (see figure 1A and figure 2) that was also different to one observed in the serum level of ADMA (see table 1). This is further supported by Xu (Neuroscince letter, 2007, 418, 201-204), who reported varying level of ADMA in plasma and brain tissue (see abstract and figure, table 1). These studies are contrary to applicants' assertion that ADMA level is homogenous throughout the body (see applicants' arguments filed 4/17/2008). Given that levels of ADMA may vary depending on values that are subjective to sample population such as age, gender, hormonal status, ethnicity, disease state, it is thus unpredictable as to how one might use any reference marker profile comprising ADMA identified in a plasma in the analysis of a biomarker profile obtained from any other biological tissue or fluid sample derived from any other pregnant women with underlying disease that influence ADMA level (kidney disease, hypertension). The specification

fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in any pregnant women of any ethnicity suffering from multiple chronic disorders to predict the risk of developing PE or risk of fetus developing IUGR if ADMA level is greater then 1.5 micro mol/L (see the discussion before). An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of predicting that a pregnant women is at risk of developing PE by measuring the level of ADMA in any tissue or fluid without reasonable expectation of success.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 1-2, 4 and 5 were rejected under 35 U.S.C. 102 (b) as being anticipated by Holden et al. (Am J Obstet Gynecol. 1998; 178(3):551-6). Applicants have amended base claim to include limitation that is not disclosed in cited art. Therefore, rejection by Holden is hereby withdrawn.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-5, 7, 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boger (WO 2002/14873, 2/21/2002, IDS), Holden et al (Am J Obstet Gynecol. 1998; 178(3):551-6, art of record).

Claims are directed to method of determining that a pregnant woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing intrauterine growth restriction (IUGR), which method comprises: (a) measuring asymmetric dimethylarginine (ADMA) in a pregnant woman at a stage of pregnancy from 4 to 25 weeks gestation; and (b)-determining that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA is greater than 1.5 micromol/L in the woman. Subsequent claims limit the stage of pregnancy to include 10-25, 15-25 weeks of gestation.

With respect to claim 1, Boger et al teach a method of detecting the risk of developing a disease including pre-eclampsia that is associated with NO metabolism by (a) measuring the level of ADMA and SDMA (see claims 1 and 9). Boger et al also disclose that preeclampsia is a disease of the NO metabolism leads to constriction of arteries which induces high blood pressure in the mother and poses a risk to the unborn child due to reduced placental perfusion (see page 2) With respect to claim 7 and 8, Boger et al contemplate measuring the ration of ADMA to SDMA in the plasma of the patient (see claim 14, 20 and 21). It is also disclosed that subject suffering from chronic condition (CHF, example 4) show ADMA concentration of 4.1 μM/L as compared to 1.0 μM/L in normal subject.

Boger teach a method of measuring ADMA in a subject to determine the risk of developing chronic condition if ADMA level is high and also contemplated to determine ADMA level in other conditions that increase high blood pressure such as PE, but Boger differed from claimed invention by not disclosing measuring ADMA level in pregnant women at a stage of pregnancy from 4 to 25 weeks gestation.

The deficiency of Boger is cured by Holden who teaches measuring plasma ADMA level in 145 pregnant women that included pregnancy of all stages (including second trimester). It is noted that Holden et al also determined the level of ADMA which is at least 0.52 μmol/L to 1.17 μmol/L depending upon stage of pregnancy. This would meet the claim limitation of measuring pregnancy at

different stage of pregnancy (4-25, 10-25 or 15-25 weeks) that is embraced by the teaching of Holden (see page 553, Figure 1 B). It is noted that Holden et al conclude that during later stage of pregnancy circulating concentrations increase and, when pregnancy is complicated by preeclampsia. Thus, method of Holden is primarily directed to study the role for ADMA in the changes in blood pressure seen in both normal and preeclampsia pregnancy (see abstract and page 555, col. 1, para. 4).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Boger by measuring the ADMA level in the pregnant women at a stage of pregnancy from 4-25 weeks gestation using the known method disclosed by Holden. It would have been prima facie obvious to one of ordinary skill in the art to combine the known methods of Boger and Holden to measure the ADMA level in a pregnant women at a stage of pregnancy from 4-25 and determine the level of ADMA to predict the risk of developing preeclampsia particularly since both generally embraced the potential of measuring ADMA level to determine the risk of developing pre-eclampsia. One who would have practiced the invention would have had reasonable expectation of success since Boger and Holden both taught method to measure ADMA level in the plasma of subject to determine if the subject is at risk of developing PE, while combining the teaching Boger and Holden would have resulted in a determining the level of ADMA that is greater then 0.54 -1.0 μM/L to establish risk of developing pre-eclampsia.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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